Resistance testing for Third Line

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Third-line ART

- Third-line ART is used when a patient has experienced virological failure on drugs from the NRTI, NNRTI and PI classes (with documented PI resistance).
- Adherence interventions should be intensified

When to Use Resistance Testing

	IAS-USA[1]	DHHS[2]	European[3]
Primary/acute	Recommend	Recommend	Recommend
Postexposure prophylaxis			Recommend*
Chronic, Rx naive	Recommend	Recommend	Recommend
Failure	Recommend	Recommend	Recommend
Pregnancy	Recommend	Recommend	Recommend
Pediatric		Recommend	Recommend

*Test source patient especially if treated with antiretroviral drugs.

1. Hirsch MS, et al. Clin Infect Dis. 2008;47:266-285.
2. November 2008 DHHS Guidelines. Available at: http://www.aidsinfo.nih.gov. Accessed November 10, 2008.
3. EACS Guidelines Version 3. Available at: http://www.eacs.eu/guide/index.htm. Accessed October 24, 2008.

Southern African HIV Clinicians Society

Failure of a boosted PI-based regimen		
Adults and children with two VL measurements >1 000 RNA copies/ml† and/or a <2 $\log_{10}$ drop in VL while on PI-based ART (measurements 3 - 6 months apart)	Recommended	Failure on PI regimens is almost always due to poor adherence. Adherence‡ issues should be addressed comprehensively between the 2 measurements. Resistance testing should be performed while the patient is on the failing regimen or within 4 weeks of discontinuation.

What information can we get?

- Resistance tests serve two purposes:
  - Adherence test.
  - If resistance mutations are present, ability to chose a regimen.

What information can we not get?

- NRTI mutations that are present only represent the current regimen.
  - Presume all first generations will not work

- NNRTI mutation are usually archived

Requirements for resistance testing

- Patient must be on ART at the time or stopped within the last 4 weeks.
- Should not be done on the first detectable viral load
- No rush – between 3-6 months.

Measures of adherence

- Self-reported, short-term adherence
- Dispensing-based long-term adherence
- Consistency of visit attendance
- Pill count-based medium-term adherence
- Electronic cap monitoring

Adherence support

- Inadequate treatment literacy
- Side effects
- Depression and other mental illnesses
- Poverty and food insecurity
- Work related issues
- Substance use
- Social problems
- Denial
- Pill burden
- Altered fertility intentions
- Conflict of opinions

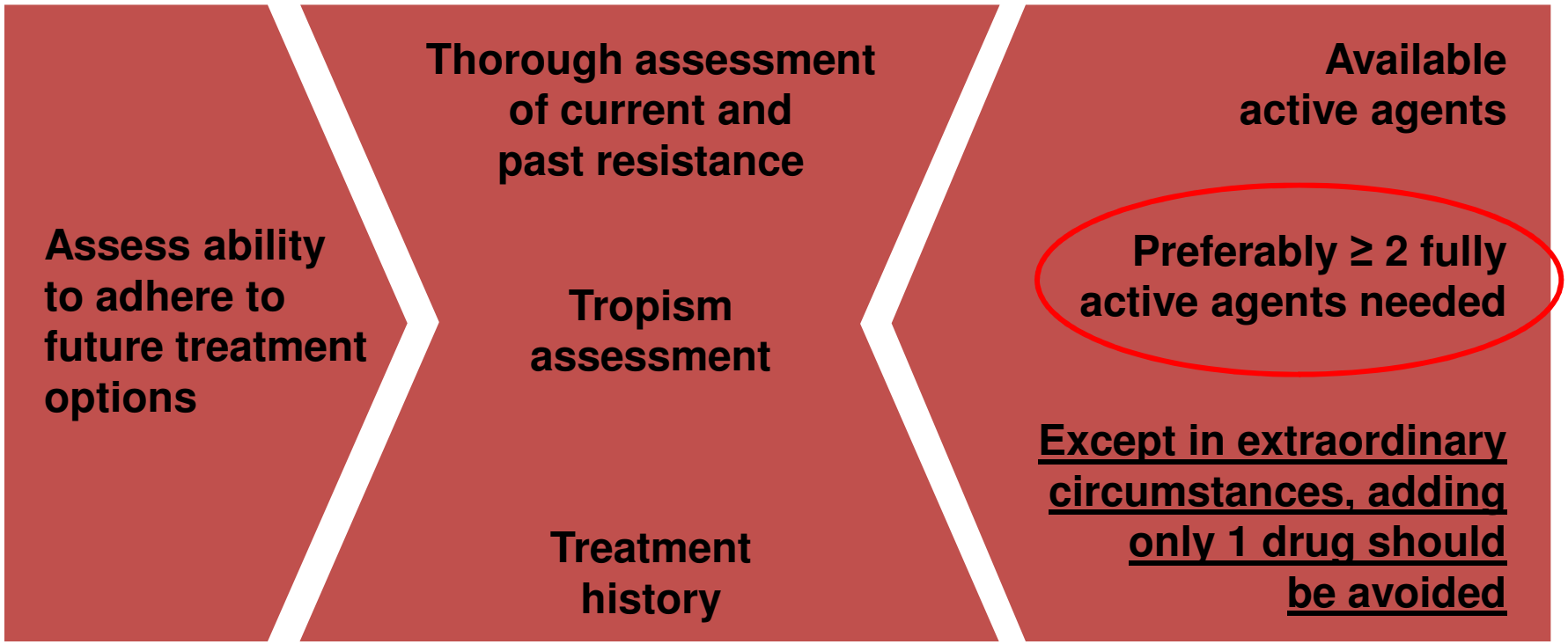
Principles

- First-generation NNRTIs have no place in third-line therapy
- A boosted PI with the broadest resistance profile should be selected
- No double ritonavir-boosted PIs.
- The addition of 3TC (or FTC) is recommended
- Consideration of the addition of other salvage drugs (e.g. RAL and/or ETV) will depend on genotype resistance test result

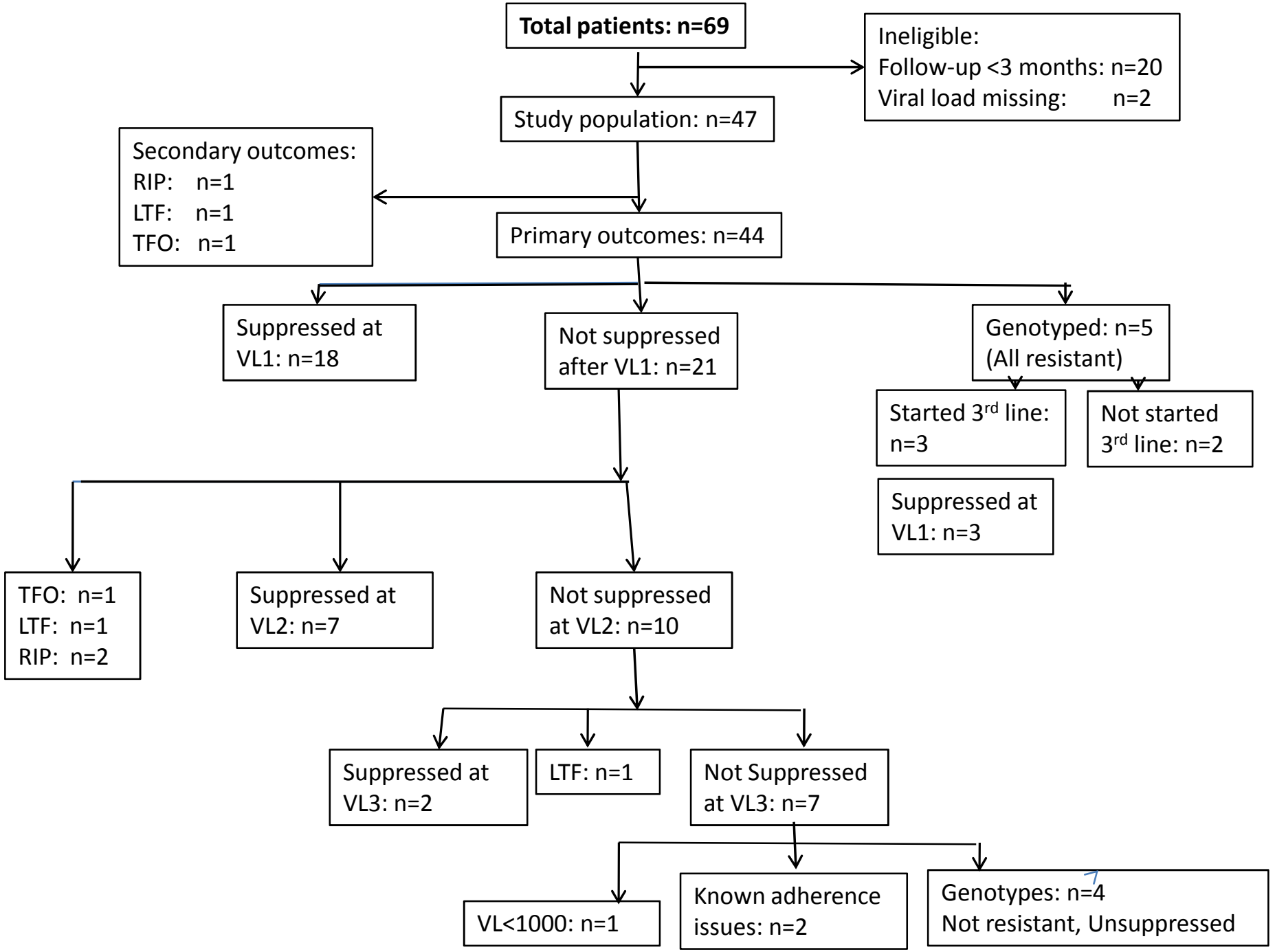
Patients who return after defaulting therapy

- Restart the same regimen and repeat HIV viral load measurements after 3 months
- Switching to a second-line regimen should be considered if the viral load is not suppressed at this point.
- AZT could be substituted for D4T.
- Do not substitute TDF

Is VL < 50 copies/mL Achievable in Tx-Experienced Patients With MDR HIV?



- Consider emerging treatment options and need for immediate enhancement of current regimen (ie, risk of clinical progression)


Total patients: n=69
Ineligible:
Follow-up <3 months: n=20
Viral load missing: n=2
Study population: n=47
Secondary outcomes:
RIP: n=1
LTF: n=1
TFO: n=1
Primary outcomes: n=44
Suppressed at VL1: n=18
Not suppressed after VL1: n=21
Genotyped: n=5 (All resistant)
Started 3rd line: n=3
Not started 3rd line: n=2
Suppressed at VL1: n=3
TFO: n=1
LTF: n=1
RIP: n=2
Suppressed at VL2: n=7
Not suppressed at VL2: n=10
Suppressed at VL3: n=2
LTF: n=1
Not Suppressed at VL3: n=7
VL<1000: n=1
Known adherence issues: n=2
Genotypes: n=4
Not resistant, Unsuppressed

- All effort should be made to address adherence problems
- “understand the failure”
- Once adherence problems are solved, resuppresion if often possible under the same treatment.
- Request a Hep B sAg for patients failing a TDF base regimen. If Hepatitis B is positive, TDF should be included in the new regimen. (TDF is active against Hepatitis B virus)

PROTEASE INHIBITOR RESISTANCE IN SOUTH AFRICAN CHILDREN WITH VIROLOGIC FAILURE

Background:

- First-line ART for children < 3 years, PI + NRTI
- Children failing ritonavir or ritonavir-boosted lopinavir (LPV/r
- Major PI resistance mutations (MPIRM)

PROTEASE INHIBITOR RESISTANCE IN SOUTH AFRICAN CHILDREN WITH VIROLOGIC FAILURE

Materials and Methods:

Pediatric HIV patients at Tygerberg Academic Hospital with virologic failure on a PI regimen.

Results: MPIRM were found in

12 of 17 patients exposed to RTV-sPI

1 of 13 patients treated with LPV/r.

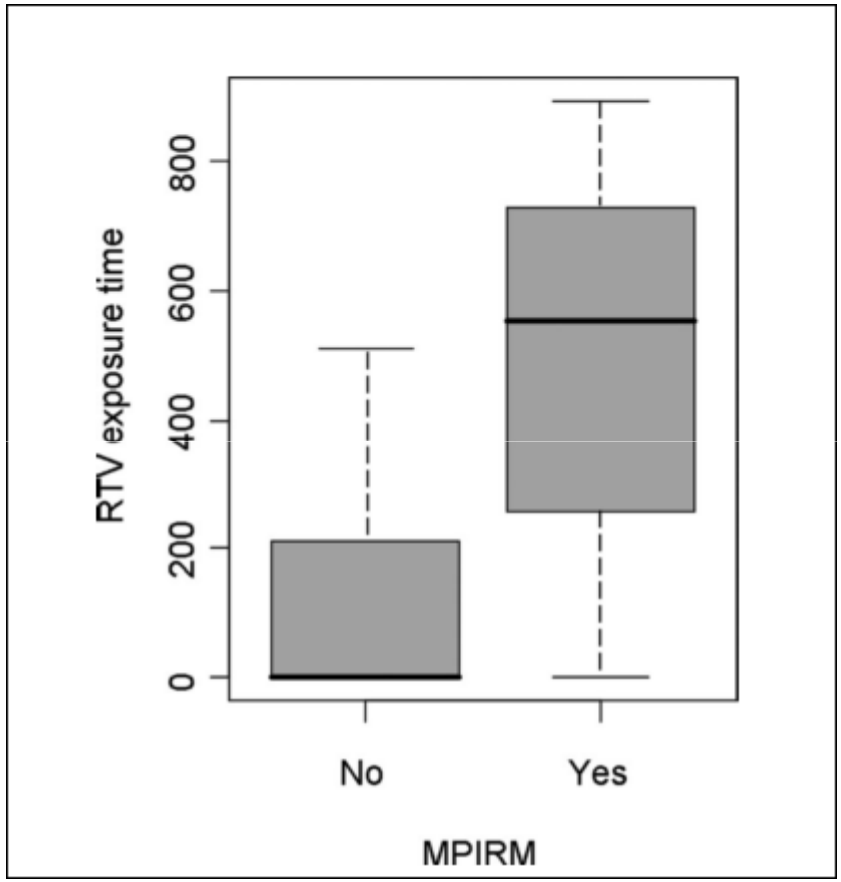
- Conclusions: RTV-sPI in infants and children poses a significant risk of MPIRM
- van Zyl, G.U. et al., 2009

TABLE 1. Main Characteristics of Study Population

Variable	LPV/r (n = 13)	RTV-sPI (n = 8)	RTV-sPI Followed by LPV/r (n = 9)	Total (n = 30)
Age at first study visit (mo)				
Median	27	20	33	28
Range	11–65	6–91	26–53	6–91
MPIRM (%)	1 (8%)	7 (88%)	5 (55%)	13 (43%)
Concurrent TB therapy (number [%])	5 (38%)	7 (88%)	7 (78%)	19 (63%)

LPV/r indicates Lopinavir co-formulated with low-dose ritonavir; RTV-sPI, RTV as single protease inhibitor; MPIRM, major protease inhibitor resistance mutations; TB, *Mycobacterium tuberculosis*.

van Zyl, G.U. et al., 2009. Protease inhibitor resistance in South African children with virologic failure. *The Pediatric infectious disease journal*, 28(12), pp.1125–7. 12, 2011].



- van Zyl, G.U. et al., 2009

HIV-1-resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor regions: a systematic review.

- Resistance rates and patterns among children in developing countries in whom antiretroviral treatment has failed.
- Outcomes in 3241 children were eligible.

- Sigaloff KC et 2011

HIV-1-resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor regions: a systematic review.

- Viruses with resistance-associated mutations were isolated from 90% (95% CI 88-93%) of children.
- The prevalence of mutations associated with
  - NRTI - 80%,
  - NNRTI -88%
  - PI- 54%.

Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir/r-Containing Antiretroviral Therapy in South Africa

Variable		Median (inter quartile range)	
	Median (inter quartile range)	No PI major mutations (n = 70)	PI major mutations (n = 5)
Age (years)	34 (29–40)		
CD_4+ T-cells/mm^3	141 (75–245)	138 (80–229)	246 (194–254)
HIV-1 RNA (copies/mL)	184,779 (8790–166,300)	61000 (15000–155000)	3260 (2200–33000)
Time on second-line (months)	16 (7–18)		

- Wallis, C.L. et al., 2011.

Resistance Mutations	*n* (%)
NRTI mutations	26 (35%)
M184V	15 (20%)
K65R	0 (0%)
Q151M	1 (1%)
TAMs	10 (13%)
NNRTI mutations	39 (52%)
K103N	16 (21%)
V106M	9 (12%)
Any PR mutations (major and minor)	67 (89%)
MajorLPV mutations	5 (7%)
M46I, L76V	1
M46I	1
L33F, I54S, V82A, I84V	1
L33F, M46I, I54V, I84V, L90M	1
M46I, I54V, L76V	1

- Major lopinavir resistance mutations were infrequent (5 of 75; 7%), indicating that drug resistance is not the main barrier to future viral suppression.

Wallis, C.L. et al., 2011. Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir/r-Containing Antiretroviral Therapy in South Africa. *AIDS research and treatment*, 2011, p.769627.